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The concentration of the elements Zn, Cu, Mg, Fe, Na, and K in human amniotic fluid during birth*

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1 Introduction

Modern biochemical analytical methods allow the determination of fetal maturity and amniocentesis allows the determination of the kinetics of important cations in the amniotic fluid (AF). It is known that the concentration of these cations changes continually during pregnancy and thus serves as an important diagnostic indicator.

Zinc: Zinc is one of the essential cations because it is a structural part and activator of about 30 enzymes and it has an indispensable function in protein biosynthesis. Deficiency states have been demonstrated in humans and animals. Zinc deficiency may cause hypoalbuminemia and growth retardation. Causes of hypozincemia in the human are genetic factors, nutritional disturbances, drugs, or disease [11]. Zinc plays an important role in the antibacterial activity of AF. Thus AF zinc levels are decreased with amniotic fluid infection. The early recognition of infections might be facilitated by recognizing disturbances in zinc concentration.

Decreased zinc intake causes disturbances of fertility and growth disturbances. The latter is particularly relevant during pregnancy. Animal experiments and clinical investigation in population with insufficient zinc intakes have shown that the symptoms of zinc deficiency as well as disturbances caused by drugs or disease respond reliably and quickly to oral or parenteral zinc therapy. Early recognition of zinc deficiency during pregnancy could lead the way to new therapeutic possibilities [12].

Copper: Copper, too, is an essential bioelement [16, 20], bound to certain functional groups of proteins such as lysyloxidase, tyrosinase, ceruloplasmin and ferrooxidase. Hypocupremia during pregnancy is a sign of placental insufficiency. The intake of drinking water with low copper content

Curriculum vitae

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may lead to congenital malformations in human embryos [15, 18].

Pregnant women with WILSON's disease (pathologic accumulation of copper) have an increased incidence of abortions [21]. Copper and zinc act as antagonist in animal metabolism [18]. An excess of zinc may lead to copper deficiency. Zinc deficiency has been observed in congenital malformations in the human [9].

The metabolism of copper and zinc in AF as determined by amniocentesis may be an important indicator for normal fetal development or the presence of congenital anomalies.

Magnesium: Magnesium, next to potassium, one of the important intracellular cations influences metabolism in many ways based on its properties of displacing calcium ions and of forming complexes with adenosine triphosphate. The symptomatology of magnesium deficiency comprises cerebral, cardio-vascular, tetanic, and visceral signs of disease [3, 7, 19]. Information on magnesium levels in AF is available only during early pregnancy [14, 17, 22, 23]. Our analysis shows that the magnesium level of AF is always lower than that in the maternal serum [17].

Iron: The iron content of AF has been determined by UYENG [22] and MISCHEL [14] in late pregnancy. Uyeng published a value of 8.5 mg% while MISCHEL found iron concentration of 200 mg% in AF from the eleventh to nineteenth week of gestation.

A normal pregnancy requires 800 mg iron daily of which 300 mg are required by fetus and placenta and 500 mg are for maternal metabolism.

Sodium and Potassium: These cations have been investigated more extensively. The sodium content in amniotic fluid is identical with that of the maternal serum [1, 5, 13]. According to BATTAGLIA [1] the sodium concentration in amniotic fluid drops during the 32nd to 35th week of gestation. During this time sodium levels are about 122–127 mEq/liter [5]. In contrast, MISCHEL [14] found values of 149 mEq/liter.

Potassium concentration in AF also corresponds to levels in the maternal serum during early pregnancy [5].

During the second half of pregnancy potassium values in amniotic fluid and serum are higher [1, 5, 8]. WIDDOWSON [23] found potassium levels in fetal urine and amniotic fluid to be equal.

2 Material and methods

For this investigation all amniotic fluid samples were obtained during delivery between the 39th and 41st week of gestation. The sample was obtained with a syringe during endoscopically controlled transvaginal amniotomy. This sampling of amniotic fluid under visual control prevents the contact of the amniotic fluid with the endoscope and contamination with blood. Any contaminated samples were not further processed. We obtained 8 ml of amniotic fluid from each of 197 women during birth. Of the patients 124 had normal pregnancies, 34 had toxemia of pregnancy; in 24 patients the AF appeared green and 15 patients smoked over 15 cigarettes daily throughout the entire pregnancy. Twin pregnancies were excluded from this study.

3 Analytical method

3.1 Preparation of samples

All samples were free of sediment, a few were slightly opaque. Depending on which element was to be assayed the samples were diluted varyingly with HERMANN's solution (MERCK, 9975). After one hour the samples were analyzed with a flamephotometer.

3.2 Matrix solution

The composition of the matrix solution can be seen in Tab. I. The separate components were added as TITRISOL® standard solution (MERCK). The matrix solution was diluted corresponding to the AF samples analysis.

3.3 Analysis

The elements were assayed with an atomic absorption spectralphotometer (Manufacturer: EVANS ELECTROSELENIUM Ltd, Halsted, Exxex; Type 240 Mark 2). The matrix solution served as control.

Tab. I. Normal values for electrolytes in amniotic fluid.

Element	Mean values from the literature mmol/liter	Normal controls mmol/liter	Matrix Solution mmol/liter	Dilution
Na^+	124.0 ± 6.2*	125.0 ± 6.2	143.5	1:100
K^+	4.3 ± 0.40*	4.16 ± 0.61	3.84	1:100
Mg^{2+}	0.55 ± 0.17*	0.55 ± 0.07	0.82	1:100
Fe^{2+}	0.0056 ± 0.0036**	0.0042 ± 0.0051	0.002	undiluted
Cu^{2+}	0.0049 ± 0.002**	0.0013 ± 0.0008	0.002	undiluted
Zn^{2+}	0.0038 ± 0.0015***	0.0024 ± 0.0022	0.015	undiluted

* Gestational age 40 weeks. Values from Johnell and Nilsson [10]. ** Gestational age 20 weeks. Values from Nusbaum and Zettner [17]. *** Gestational age 20 weeks. Values from Clark, H. C. [4].

Tab. II. Comparison of Na, K and Mg concentrations in amniotic fluid of normal controls and at-risk pregnancies.

Element mmol/liter		Control Group	Toxemia	Green AF	Smokers
Na	$\bar{x}$	125.3	125.3	127.0	127.9
	SD	6.2	9.7	5.0	7.2
	n	124	34	24	15
	5	–	0.311	1.249	1.514
K	$\bar{x}$	4.16	4.09	4.37	4.93
	SD	0.61	0.64	0.64	2.42
	n	124	34	24	15
	5	–	0.558	1.562	2.930
Mg	$\bar{x}$	0.551	0.545	0.779	0.559
	SD	0.072	0.090	0.384	0.151
	n	124	34	24	15
	t	–	0.464	6.151	0.342

Tab. III. Comparison of zinc concentration in the amniotic fluid of controls and at-risk pregnancies.

Zinc Concentration mmol/liter	Control N	Toxemia N	Green Amniotic Fluid N	Smokers N	Sum
0 –0.001	55	10	1	5	71
0.002–0.004	53	15	13	9	90
0.005–0.01	16	9	10	1	36
Sum	124	34	24	15	197

In order to eliminate analytical errors of non-specific absorption the principle of the addition method was used when analysing undiluted samples for iron, zinc and copper.

Tab. IV. Comparison of copper concentration in the amniotic fluid of controls and at-risk pregnancies.

Copper Concentration mmol/liter	Control N	Toxemia N	Green Amniotic Fluid N	Smokers	Sum
0 –0.001	99	20	3	11	133
0.002–0.003	21	9	13	3	36
0.004–0.005	4	3	7	1	14
Sum	124	32	23	15	194

4 Statistical evaluation of electrolyte levels in amniotic fluid

The results list values for arithmetic mean ($\bar{x}$), standard deviation (SD), and the analysis of variance (student -t Test). For $t > 2.0$ there is a significant difference ($p < 0.05$) from the controls.

For cations Na, K and MG the statistical evaluation of the analytical results shows a normal distribution allowing the use of the t-test. The cations Zn, Cu and Fe behaved differently; therefore, the χ^2-test was used and the results are presented in Tabs. III through VI.

From a table of contingencies the following χ^2 values are calculated:

for zinc, $\chi^2 = 22.39$
for copper, $\chi^2 = 44.78$
for iron, $\chi^2 = 27.70$

With a degree of freedom of 6 the critical value for χ^2, if $p \leq 0.05$, is 12.6. Thus, the distribution of zinc and copper concentrations in amniotic fluid are significantly different from the entire sample. A comparison of the various pathologic pregnancies and normal controls allows the following conclusions in Tab. VI and VII when analyzed with the χ^2 test (df = 2, critical χ^2 value: 6.0 for $p \leq 0.05$).

As seen in Tab. I, the values for sodium, potassium and magnesium correspond well with those of other authors [4, 10, 17]. In contrast, our means for the normal controls for zinc, copper and iron vary considerably from data in the literature. Values published by others [2, 4, 11, 12, 17] are considerably higher. This may be due to differences in analytical methodology or due to geographically different nutritional factors. Our results have been verified by appropriate analyses of reference samples and recovery tests. This includes copper which was found to be higher by a factor of 3.6 by NUSBAUM and ZETTNER [17] than the copper level of our control group. Considering the generally accepted fact that the zinc concentration in tissue and body fluids is considerably higher than that of copper, the levels found in the literature appear to be too high. The relevant publications offer only a few comparable values; thus, a detailed critical discussion of the existing differences cannot be made. Because of this uncertainity we have used for our results the same reference data which were used in our study "Pathobiochemistry of Mineral and Trace Elements in Pregnant Women and their Neonates." Thus there have been identical conditions for the evaluation of analytical results within our studies.

Tab. V. Comparison of iron concentration in the amniotic fluid of controls and at-risk pregnancies.

Iron Concentration mmol/liter	Control N	Toxemia N	Green Amniotic Fluid N	Smokers	Sum
0 –0.002	48	12	5	5	70
0.003–0.005	59	5	7	6	77
0.006–0.017	14	13	11	4	42
Sum	121	30	23	15	189

4.1 Comparison of cation levels in AF from pathologic pregnancies

4.1.1 Sodium

The course of pregnancy and exogenous factors do not influence sodium concentration of AF. The mechanisms of sodium kinetics are regulated in a way which prevents any disturbances.

Tab. VI. Statistical evaluation of zinc, copper and iron concentrations in amniotic fluid of normal controls and at-risk pregnancies.

	χ^2	Zinc Significance	χ^2	Copper Significance	χ^2	Iron Significance
Toxemia	4.56	not significant	4.80	not significant	19.41	significant
Green Amniotic Fluid	18.64	significant	44.81	highly significant	17.79	significant
Smokers	1.70	not significant	0.58	not significant	2.65	not significant

Tab. VII. Distribution of APGAR scores of newborns in varying types of pregnancies.

APGAR Score	Control Group N	%	Toxemia N	%	Green Amniotic Fluid N	%	Smokers N	%	Sum N	%
≤8	48	39	14	41	15	63	4	27	81	41
>8	76	61	20	59	9	37	11	73	116	59

4.1.2 Potassium

In contrast, the potassium level in pregnancy women with green amniotic fluid rises by about 5%; this may still be within normal variability. A significant increase of potassium by about 15% in comparison to controls is seen in smokers. All risk should be comprehensively evaluated factors before assuming that there is a correlation with increased pregnancy risk. It should be noted that GIRAUD [6] observed a high variability of electrolyte concentrations towards the end of pregnancy. The concentration of potassium varies between 2.5 and 5.5 mmol/liter for 90% confidence range. This will be dealt with in more detail elsewhere.

4.1.3 Magnesium

A significantly increase concentration of magnesium is found in green amniotic fluid. The deviation from normal values is considerably outside the biological variability. Thus, it is considered an indication for a pathologic process and corresponds to the loss of magnesium in whole blood and serum. A determination of the magnesium balance might give information on the extent of severe losses of magnesium during pregnancy and to what exteht the redistribution to the various compartments occur. In addition the interpretation of the findings must consider the production of amniotic fluid, its density, the fetal excretion and absorption processes. However, to date studies on magnesium concentration in AF have not shown any specific correlations between normal and pathological pregnancies unlike magnesium values in blood and serum of pregnant women.

4.1.4 Zinc, copper, iron

As was seen for magnesium the concentration for these three cations is above normal in pathologically stained amniotic fluid. The newborns with an APGAR score of 8 are predominately in the group with green amniotic fluid. This might allow the conclusion that intestinal absorption of the fetus is limited or that the cation equilibrium for these elements is disturbed and has lead to an intracellular deficiency for essential biometals with an impaired physiologic status of the newborn. This corresponds to the frequently seen significantly decreased zinc and copper values in blood and serum of newborns and infants with manifest symptoms of disease. Even assuming that there are fetal metabolic priorities vis-à-vis the maternal metabolism, the supply of the fetus with vital and irreplaceable bioelements via the placental may be insufficient or uncertain. APGAR and other authors have pointed out the substitution of bioelements during pregnancy and have made well founded recommendations.

Summary

In order to determine the influence of the course of pregnancy and exogenous factors on the quantitative distribution of the cations sodium, potassium, magnesium, zinc, copper and iron in amniotic fluid, these cations were assayed in the amniotic fluid of 197 pregnant women with atom absorption spectrophotometry. There were 124 normal pregnancies, 34 with toxemia, 23 with green amniotic fluid and 15 smokers.

The results of sodium, potassium, and magnesium concentrations correspond well with values found by other authors. In contrast, normal mean values for zinc, copper, and iron are different from those published to date. The course of pregnancy and exogenous factors do not influence sodium concentration in the amniotic fluid. Smokers when compared with normal controls showed a significantly increased potassium in green amniotic fluid. Magnesium concentration in green amniotic fluid is also significantly increased. Similarly, values for zinc, copper and iron in pathologic amniotic fluids was significantly above normal means.

This corresponds to the significantly decreased in copper and zinc values in blood and serum of newborns and infants in various disease states. The essential elements zinc, copper and magnesium are important both for the course of pregnancy as well as for the development of fetus and newborn.

APGAR and others have indicated the importance of the replacement of bioelements, especially zinc, during pregnancy. We also may conclude that during pregnancy essential cations should be determined in serum or better yet in whole blood and amniotic fluid of the mother in order to avoid the pathophysiologic consequences of severe cation disturbances in mother and infant by appropriate replacement therapy.

Keywords: Amniotic fluid, cation concentration, cation replacement, copper, EPH-gestosis, iron, magnesium, potassium, pregnancy, sodium, zinc.

Zusammenfassung

Über die Konzentration der Elemente Zn, Cu, Mg, Fe, Na und K im menschlichen Fruchtwasser unter der Geburt

Zur Differenzierung des Einflusses des Schwangerschaftsverlaufes und exogener Noxen auf die quantitative Verteilung der Kationen Natrium, Kalium, Magnesium, Zink, Kupfer und Eisen im Fruchtwasser, wurden die aktuellen Konzentrationen im Fruchtwasser von 197 Schwangeren mittels Atomabsorptionsspektrophotometrie bestimmt. Das Gesamtkollektiv wurde in 4 Gruppen eingeteilt: 124 normale Schwangerschaften, 34 Gravide mit EPH-Gestose, 23 Schwangere mit grünem Fruchtwasser und 15 Raucherinnen.

Die ermittelten Kationenspiegel zeigen in Bezug auf die Natrium-, Kalium- und Magnesiumkonzentrationen eine gute Übereinstimmung mit den Ergebnissen anderer Autoren; im Gegensatz dazu weichen die von uns ermittelten Normmittelwerte bei den Kationen Zink, Kupfer und Eisen deutlich von den Literaturdaten ab. Der Graviditätsverlauf und exogene Faktoren sind ohne Einfluß auf die Natriumkonzentration des Fruchtwassers. Hingegen wird bei Raucherinnen, im Vergleich mit der Kontrollgruppe, eine signifikante Erhöhung des Kaliumwertes im grünen Fruchtwasser gemessen. Auch der Magnesiumspiegel ist im grünen Fruchtwasser außerhalb der biologischen Streubreite erheblich erhöht. Ähnlich wie bei den Magnesiumwerten liegen die Zink-, Kupfer- und Eisenspiegel im verfärbten Fruchtwasser signifikant über den Normmittelwerten.

Diese Befunde verlaufen parallel zu den nahezu regelmäßig festzustellenden signifikant erniedrigten Zink- und Kupferwerten im Vollbut und Serum von Neugeborenen und Kleinkindern mit manifesten Krankheitssymptomen oder mit einer verminderten Vitalität. In diesem Zusammenhangwird auf die Bedeutung der essentiellen Elemente Zink, Kupfer und Magnesium sowohl für den Verlauf der Schwangerschaft, als auch für die Entwicklung des Feten und des Neugeborenen hingewiesen.

APGAR und andere haben auf den Stellenwert der Substitution von Bioelementen, insbesondere von Zink während der Schwangerschaft, hingewiesen und diesen Sachverhalt ausführlich durch quantitative Messungen und morphologische Untersuchungen belegt. Außerdem können wir aus unseren Untersuchungen die Schlußfolgerung ableiten, daß während der Gravidität essentielle Kationen im Serum, besser im Vollblut und im Fruchtwasser der Mutter routinemäßig bestimmt werden sollten, um durch entsprechende Substitution die pathophysiologischen Folgen schwerer Kationenentgleisungen für Mutter und Kind zu vermeiden.

Schlüsselwörter: Eisen, EPH-Gestose, Fruchtwasser, Kalium, Kationenkonzentration, Kationensubstitution, Kupfer, Magnesium, Natrium, Schwangerschaft, Zink.

Résumé

De la concentration des éléments Zn, Cu, Mg, Fe, Na, et K dans le liquide amniotique human pendant l'accouchement

Afin d'apprécier l'influence de l'évolution de la grossesse et des éffets externes sur la répartion quantitative des cations Na, K, Mg, Zn, Cu et Fe dans le liquide amniotique, nous avons déterminé les concentrations actuelles des cations cités chez 197 parturientes à l'aide de spectrophotométrie d'absorption d'atomes. Les patientes ont été réparties dans 4 groupes: 124 grossessses normales, 34 toxémiques, 23 gravides au liquide amniotique teinté et 15 femmes qui fument.

Les valeurs observées pour les cations Na, K et Mg montraient une bonne corrélation avec les valeurs observées par d'auteurs; par contre nos valeurs de Zn, Cu et Fe se différencient nettement des valeurs de la littérature. L'évolution de la grossesse et les facteurs exogènes sont sans répercussion sur les valeurs de Na du liquide amniotique. Par contre chez les fumeuses, l'on note une augmentation significative de la valeur de K dans le liquide teinté. De même la valeur de Mg sort dans le liquide teinté de la zone de variabilité biologique et est très augmenté. De même que les valeurs de Mg, celles de Zn, Cu et Fe dans le liquide amniotique pathologique sont au dessus des valeurs moyennes normales de façon significative.

Cet état correspond à la diminution quasi constante et significative des valeurs de Zn et Cu dans le sang et sérum de nouveaux-nés et petits enfant malades ou à la vitalité diminuée. Nous renvoyons à ce propos à l'importance des élements éssentiels Zn, Cu et Mg aussi bien pour l'évolution de la grossesse que pour le dévéloppement du foetus et du nouveau-né.

APGAR et d'autres ont insisté sur l'importance de la substitution des bioéléments, en particulier du Zn pendant la grossesse; ils ont prouvé ce fait par des mesures quantitatives et des investigations morphologiques. De plus nous pouvons tirer de nos observations la conclusion que les cations essentiels devraient être déterminés de façon systématique dans le sang et le liquide amniotique afin d'éviter, par des substitutions corréspondantes, les suites pathophysiologiques pour la mère et le foetus liées aux déficits cationiques sévères.

Mots-clés: Concentration cationique pendant la grossesse, facteurs exogènes, grossesse normale, liquide amniotique teinté, Na, K, Mg, Zn, Cu, Fe-substitutions cationiques.

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